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Can PCO_2 be a mortality predictor in COVID-19 patients?

PCO_2, COVID-19 hastalarında mortalite belirteci olabilir mi?

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ABSTRACT

Aim: The clinical course of Corona Virus Disease 2019 (COVID-19) infection is ranging from asymptomatic to moderate and severe disease with low survival rates. Therefore, reliable prediction of COVID-19 mortality and identification of contributing factors would allow targeted therapies for high-risk individuals. We aimed to determine whether partial carbon dioxide (PCO_2) concentrations could predict mortality in patients treated in the intensive care unit (ICU).

Material and Method: Acute Physiology and Chronic Health Evaluation (APACHE -2) scores, ferritin, lymphocyte count, neutrophil lymphocyte ratio (NLR), PCO_2, partial oxygen concentration to inspired oxygen fraction (P/F) ratio were retrospectively determined and were compared between survivors and non-survivors.

Results: The mean APACHE-2 value was higher in Group Non-survivors than in Group Survivors. Patients in Group Non-survivors were significantly older than those in Group Survivors (p=0,012). From day 7, low baseline lymphocyte counts were significant for mortality (p=0,046). NLR was also high at ICU admission, and it was significant for mortality from the 7^{th} day (p=0.022). From day 10, PCO_2 and ferritin levels increased in Group Non-survivors. The P/F ratio increased with treatment in both groups during the first 10 days, and after day 13, the increase continued in Group Survivors, whereas the values decreased in Group Non-survivors. We found that PCO_2 concentrations in patients at ICU admission were as expected and that the increase in PCO_2 could predict mortality along with increased ferritin levels, older age, high APACHE scores, low lymphocyte count, elevated NLR and high P/F ratio.

Conclusion: This study showed that in patients with COVID -19, an increase in PCO_2 concentration can predict mortality along with increased ferritin levels, older age, high APACHE scores, low lymphocyte count, elevated NLR and high P/F ratio.

Keywords: COVID-19, mortality, pneumonia, PCO_2

ÖZ

Amaç: Corona Virüs Hastalığı 2019 (COVID-19) enfeksiyonunun klinik seyri, asemptomatikten düşük sağkalım oranlarına sahip orta ve şiddetli hastalığa kadar değişmektedir. Bu nedenle, COVID-19 mortalitesinin güvenilir bir şekilde tahmin edilmesi ve katkıda bulunan faktörlerin belirlenmesi, yüksek riskli bireyler için hedefe yönelik tedavilere olanak sağlayacaktır. Yoğun bakım ünitesinde (YBÜ) tedavi edilen COVID-19 hastalarında kısmi karbon dioksit (PCO_2) konsantrasyonlarının mortaliteyi tahmin edip edemeyeceğini belirlemeyi amaçladık.

Gereç ve Yöntem: Akut fizyoloji ve kronik sağlık değerlendirmesi (APACHE -2) skorları, ferritin, lenfosit sayısı, nötrofil lenfosit oranı (NLR), PCO_2, kısmi oksijen konsantrasyonu/inspire edilen oksijen fraksiyon oranı (P/F) hasta dosyaları taranarak belirlendi ve hayatta kalanlarla ölen hastalar karşılaştırıldı.

Bulgular: Ortalama APACHE-2 değeri ölen grupta sağ kalanlardan daha yüksekti. Ölen hastalar, sağ kalanlardan anlamlı olarak daha yaşlıydı (p=0,012). 7. günden itibaren, düşük bazal lenfosit sayıları mortalite için önemliydi (p=0,046). NLR, yoğun bakıma yatışta da yüksekti ve 7. günden itibaren mortalite açısından anlamlıydı (p=0,022). 10. günden itibaren, ölen grubunda PCO_2 ve ferritin seviyeleri arttı. İlk 10 gün boyunca her iki grupta da tedavi ile P/F oranı arttı ve 13. günden sonra artış sağ kalanlarda devam ederken, ölen grubunda değerler azaldı.

Sonuç: Bu çalışma, COVID-19 hastalarında PCO_2 konsantrasyonundaki artışın, yüksek ferritin seviyesi, ileri yaş, yüksek APACHE skorları, düşük lenfosit sayısı, yüksek NLR ve yüksek P/F oranı ile birlikte mortaliteyi öngörebileceğini göstermiştir.

Anahtar Kelimeler: COVID-19, PCO_2, mortalite, pnömoni

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INTRODUCTION

Severe acute respiratory syndrome-Corona virus-2 (SARS-CoV-2), a member of the coronavirus family, causes Corona virus disease 2019 (COVID-19). World Health Organization (WHO) declared COVID-19 a pandemic on 11 March 2020. The COVID-19 pandemic affected over 400 million people worldwide and caused close to 6 million deaths (1). The disease's spread is worrisome because it has been linked to respiratory illnesses. Fever, cold, cough, shortness of breath, and diarrhea are among the symptoms. In severe circumstances, pneumonia can cause death. Because the disease is rapidly spreading, it is urgently required to predict its fatality rate and assess the related hazards. The growth of such an epidemic has also produced issues for healthcare personnel and public health communities because of the disease's uncertainties, including transmission medium, treatment, recovery rates, and risk prediction (2).

The clinical course of SARS-CoV-2 infection has revealed significant heterogeneity, ranging from asymptomatic to moderate and severe disease types with low survival rates. In particular, it is difficult to predict clinical outcomes for patients with a wide range of symptoms. This issue complicates prognostication and management of COVID-19 patients, especially in disease epicenters with high patient volumes. Therefore, reliable prediction of COVID-19 mortality and identification of contributory factors would allow focused treatments in high-risk individuals (3). Predicting patient mortality helps with the classification and allocation of resources. Commonly used scores for mortality and morbidity, Modified Early Warning Score (MEWS), Acute Physiology and Chronic Health Evaluation (APACHE II), Simplified Acute Physiology Score (SAPS II), sequential organ failure assessment score (SOFA), and quick SOFA (qSOFA), provide a rough estimate. However, the specificity and sensitivity of these tools are limited for patients with COVID-19 (4). In a large-scale study in Wuhan, China, epidemiological, clinical, and laboratory characteristics differed significantly between survivors and non-survivors. For example, older age, dyspnea, chest pain and unconsciousness were more common in healed patients who died. Alanine aminotransferase (ALT), aspartate aminotransferase (AST), creatinine (Cr), ferritine, creatine kinase (CK), lactate dehydrogenase (LDH), troponin I (TnI), N-terminal pro-brain natriuretic peptide (NT proBNP) and D-dimer concentrations were higher and lymphocyte count lower than those in survivors in patients who died (5).

Although the prognosis of COVID-19 pneumonia can be predicted by various biomarkers and scoring methods described above, a parameter that directly predicts mortality has not yet been demonstrated. In our experience in the intensive care unit (ICU), we have seen that the increase in PCO_2 concentration above a certain level leads to mortality. This study aimed to investigate whether PCO_2 concentration can predict mortality by comparing it with ferritin, lymphocyte count, neutrophil lymphocyte ratio (NLR), and partial oxygen concentration to inspired oxygen fraction (P/F) ratio, in covid-19 patients treated in the ICU.

MATERIAL AND METHOD

After approval of Ethical Committee of the Erzurum Regional Education and Research Hospital, the files of all COVID-19 patients followed in Erzincan Binali Yıldırım University Mengucek Gazi Training and Research Hospital were scanned retrospectively. Patients aged 18-100 years with a diagnosis of COVID -19 were included in the study. Patients with a COPD diagnosis and patients who died within the first 16 days were excluded from the study. The patients were divided into two groups as survivors and non-survivors. The male and female genders were equal. Along with the demographic data of the patients, arterial PCO_2, APACHE II scores, NLR, ferritin levels, arterial partial oxygen concentration (PO_2), fraction of inspired oxygen (FIO_2) , P/F ratio were recorded. The results of the first 16 days of the patients were evaluated.

Statistical Analysis

The Statistical Package for the Social Sciences (SPSS) version 26 was used for data analyses (IBM Corp., Armonk, NY). The Mann Whitney U-test was used to determine between groups differences. The repeated measures ANOVA was used for determining pairwise comparison and $P<0.05$ was defined as statistically significant. To further evaluate the link between PCO_2, ferritin, lymphocyte count, NLR, P/F ratio and mortality, the receiver operating characteristic curve (ROC) was plotted, and the area under the curve (AUC) was obtained. The cutoff values were designed to be as high as possible while maintaining a consistent mix of sensitivity and specificity. Additionally, a binary logistic regression was utilized to assess the relationship with mortality.

RESULTS

Data from 120 patients were analyzed. Sixty consecutive survivors and non-survivor patients were enrolled in the study (Group Survivors, n=60, Group Non-survivors, n=60). Demographic data are summarized in **Table 1**.

PCO_2 Analyses

Time-dependent variation in PCO_2 concentrations was different in Survivor and Non-survivor Groups (**Figure 1**). A positive correlation was found between PCO_2 concentration and mortality (r= 0.333, P= 0.009), which was observed from the 11th day. The strong correlation value calculated on the 16th day was (r=0.732, p=0.00). As a result of the ROC analysis performed to determine mortality, diagnostic discrimination was found from the 11th day (p=0.013) (**Figure 2**.). ROC curve analysis was used to compare the performance of PCO_2 as predictors of mortality. PCO_2 was a better predictor of mortality with an AUC of 0.91 (95% CI: 0.829-0.996) at day 16, and the optimal cut-off value for predicting mortality was 47 mmHg with a sensitivity of 90% at the expense of a specificity of 83.3%, as shown in **Table 2**.

Table 1. Demographic data

	Survivors	Non-survivors	p-value
Age (Years)			p= 0.012
Mean	66.33	73.83	
Youngest	21	48	
Oldest	81	88	
Gender			
Male	26	32	
Female	34	28	
APACHE-2 Score			p=0.09
Mean	26.93	30.90	
Lowest	15	18	
Highest	42	44	

APACHE-2: Acute Physiology and Chronic Health Evaluation

Ferritin Analyses

Ferritin levels over time were different in the death and survival groups (**Figure 1**.). A positive correlation was found between ferritin and mortality (r= 0.353, P= 0.006), which was observed from the 10th day. As a result of the ROC analysis performed to determine mortality, diagnostic distinctiveness was found from the 10-day measurement (p=0.011) (**Figure 2**.). ROC curve analysis was used to compare the performance of ferritin, as predictors of mortality. Ferritin was a better predictor of mortality with an AUC of 0.81 (95% CI: 0.693-0.927) at day 16, and the optimal cut-off value for predicting mortality was 648,5 ng/mlL with a sensitivity of 76.7% at the expense of a specificity of 66.7%, as shown in **Table 2**.

Lymphocyte Analyses

Lymphocyte count over time were different in the death and survival groups (**Figure 1**.). A negative correlation was found between lymphocyte count and mortality (r= 0.258, P= 0.046), which was observed from the 7th day. As a result of the ROC analysis performed to determine mortality, diagnostic distinctiveness was found from the 7th day measurement (p=0.048) (**Figure 2**.). ROC Curve analysis was used to compare the performance of lymphocyte count as predictors of mortality. Lymphocyte was a better predictor of mortality with an AUC of 0.828 (95% CI: 0.719-0.938) at day 16, and the optimal cut-off value for predicting mortality was $0,65x10^9$/L with a sensitivity of 86% at the expense of a specificity of 66%, as shown in **Table 2**.

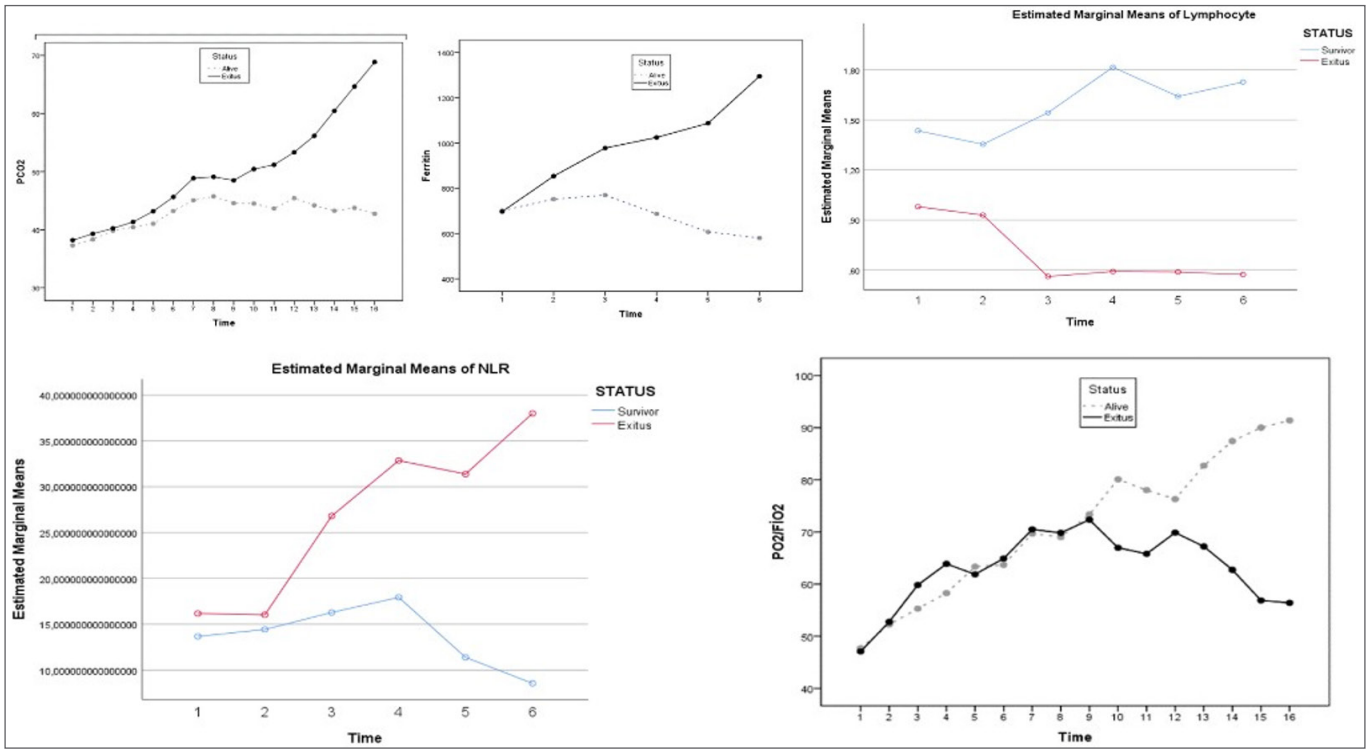

Figure 1. Time-dependent variations

Table 2. Area Under the Curve and Cut-off values

Test Result Variable(s)	Area	Std. Errora	Asymptotic Sig.b	Asymptotic 95% Confidence Interval		Cut-off	Sensitivity %	Specifity %
				Lower Bound	Upper Bound			
PCO_2 11th day	.687	.069	.013	.552	.822	49.5	%73.3	%80
PCO_2 12th day	.715	.071	.004	.576	.854	47.0	%90	%83.3
PCO_2 13th day	.815	.057	.000	.703	.927	54.5	%80	%90
PCO_2 14th day	.869	.053	.000	.766	.973	56.5	%83.3	%93.3
PCO_2 15th day	.887	.047	.000	.795	.979	49.5	%73.3	%80
PCO_2 16th day	.912	.043	.000	.829	.996	47.0	%90	%83.3
Ferritin 10th day	.691	.070	.011	.553	.828	648.5	%76.7	%66.7
Ferritin 13th day	.750	.066	.001	.622	.878	692.5	%76.7	%73.3
Ferritin 16th day	.810	.059	.000	.693	.927	1003	%76.7	%86.7
Lymphocyte 7th day	.649	.071	.048	.510	.788	0.54	%60	%60
Lymphocyte 10th day	.702	.070	.007	.565	.839	0.71	%60	%70
Lymphocyte 13th day	.750	.064	.001	.624	.876	0.72	%60	%80
Lymphocyte 16th day	.828	.056	.000	.719	.938	0.65	%86	%66
NLR 7th day	.670	.071	.024	.532	.808	18.58	%70	%66
NLR 10th day	.709	.068	.005	.576	.842	18.46	%73	%73
NLR 13th day	.862	.051	.000	.763	.961	20.75	%70	%83
NLR 16th day	.884	.047	.000	.793	.976	20.16	%66	%93
P/F 13th day	.734	.065	.002	.606	.862	66.5	%66.7	%76.7
P/F 14th day	.864	.047	.000	.772	.956	67.5	%76.7	%86.7
P/F 15th day	.926	.032	.000	.863	.989	67.75	%86.7	%83.3
P/F 16th day	.941	.028	.000	.887	.996	69.5	%86.7	%86.7

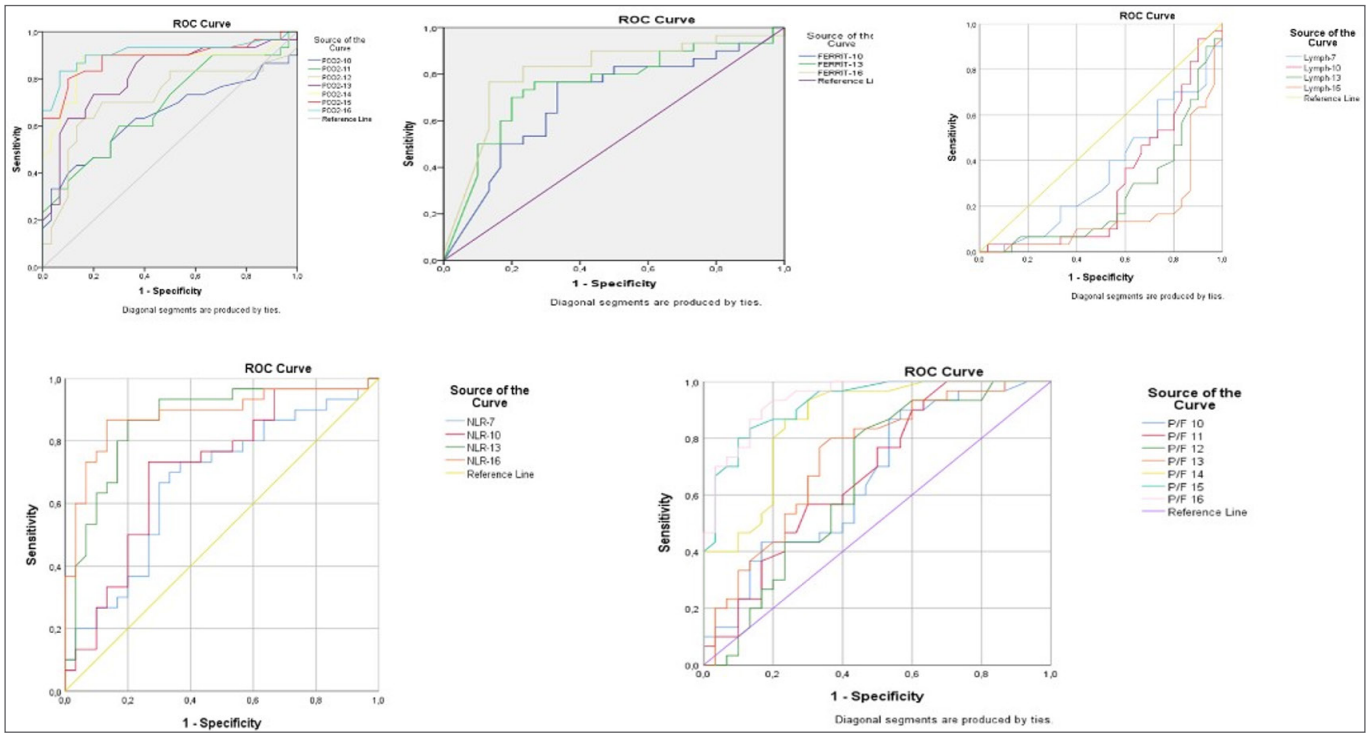

Figure 2. ROC curves

Neutrophil Lymphocyte Ratio (NLR)

NLR over time were different in the death and survival groups (**Figure 1**.). A positive correlation was found between NLR and mortality (r= 0.294, P= 0.022), which was observed from the 7th day. As a result of the ROC analysis performed to determine mortality, diagnostic distinctiveness was found from the 7th day measurement (p=0.024) (**Figure 2**.). ROC curve analysis was used to compare the performance of NLR as predictors of mortality. NLR was a better predictor of mortality with an AUC of 0.884 (95% CI: 0.793-0.976) at day 16, and the optimal cut-off value for predicting mortality was 18,46 with a sensitivity of 73% at the expense of a specificity of 73%, as shown in **Table 2**.

P/F Ratio Analysis

Time-dependent variation in P/F ratio was different in Survivor and Non-survivor Groups (**Figure 1**.). A negative correlation was found between PO_2/FO_2 ratio and mortality (r=0.348, P=0.006), which was observed from the 13th day. As a result of the ROC analysis performed to determine mortality, diagnostic discrimination was found at 10, 11, 13, 14, 15 and 16 time points. This difference became continuous from the 13th-day measurement (p=0.02) (**Figure 2**.). ROC curve analysis was used to compare the performance of P/F ratio as predictors of mortality. P/F ratio was a better predictor of mortality with an AUC of 0.941 (95% CI: 0.887-0.996) at day 16, and the optimal cut-off value for predicting mortality was 69.75 with a sensitivity of 86.7% at the expense of a specificity of 86.7%, as shown in **Table 2**.

We performed a logistic regression model to analyze PCO_2 concentration, Lymphocyte count, serum ferritin level, NLR and P/F ratio as independent predictors of mortality (**Table 3**). Age (OR: 1.098; 95% CI: 1.014-1.190; p=0.021), ferritin (OR: 1.004; 95% CI=1.000-1.008; p=0.037), PCO_2 concentration (OR: 1.335; 95% CI: 1.03-1.729; p=0.029), lymphocyte count (OR: 1.068; 95% CI: 1.01-1.464; p=0.006), NLR (OR: 1.151; 95% CI=1.064-1.246; p=0.00), P/F ratio (OR: 1.083; 95% CI=1.000-1.172; p=0.05) remained independently associated with mortality.

DISCUSSION

COVID-19 is leading to mortality since the day it started. Although many different treatment protocols have been tried worldwide, the rate of severe morbidity and mortality has not been sufficiently reduced. Most of the patients in the ICU are hospitalized due to respiratory failure and hypoxia. All studies on COVID-19 report that age is a risk factor. Parallel to this, in our study, the mortality rate was statistically higher in elderly patients. The process that starts with hypoxia progresses to ventilation disorder when there is no response to treatment, which increases the PCO_2 values. In our intensive care experience, we found that the patients entered an arduous process to reverse with increased PCO_2 values. Unfortunately, most of these patients died.

This study was based on the hypothesis that the PCO_2 value measured in arterial blood gas could be a mortality indicator, and our hypothesis was confirmed. The PCO_2 values of the patients who died increased on the 11th day of ICU hospitalization, and the optimal cut-off value for predicting mortality was 47 mmHg with a sensitivity of 90% at the expense of a specificity of 83.3%. In the literature review, we have not yet seen any comment on the contribution of PCO_2 value to mortality. This study in 120 ICU patients will be the first in this regard. Wang et al. (6) found a mean PCO_2 concentration of 34 mmHg in 138 patients. In contrast to our study, only 36 (26.1%) of the patients in their study were ICU patients. Vélez-Paez et al. (7) found that a PCO_2 concentration of 49.34 mmHg and above was associated with mortality, which is close to our value (p=0.026).

The cut-off values for lymphopenia ranged from 0.5 to 1.5×10^9/L in a meta-analysis by Brandon et al. (8) that included twenty-one studies reporting the rate of lymphopenia by disease severity. The presence of lymphopenia at diagnosis was associated with a greater than 4-fold increased likelihood of progression to severe disease. The same meta-analysis reported that the presence of lymphopenia increased mortality by up to 4-fold and by up to 12 times in severe lymphopenia ($< 0.5\times10^9$/L). In our study, lymphopenia was associated with mortality, similar to the meta-analysis, and the cutoff value was 0.65×10^9/L with a sensitivity of 86% and a specificity of 66%.

According to recent research, inflammatory cytokines, chemokines, and NLR are related to disease severity and are indicators of cytokine storm intensity. NLR, which primarily represents the extent of systemic inflammation, has been associated with pathogenicity in COVID -19 patients. High NLR has been associated with severe clinical symptoms as well as hospitalization in the intensive care unit, recovery, and situations such as discharge and mechanical ventilation (9). In their study, Asghar et al. (10) calculated the AUC value of NLR in deceased patients to be 0.860 and found it to be a strong predictor of mortality. Similarly, the AUC value in our study was 0.884 and the optimal cut-off value for predicting mortality was 18,46 with a sensitivity of 73% at the expense of a specificity of 73%.

Table 3. Analysis of independent predictors of mortality in COVID-19 patients in ICU using a logistic regression model

Parameters	B	SE	Wald	p value	Odds ratio	Lower 95% CI	Upper 95% CI
Age	0.094	0.041	5.311	0.021	1.098	1,014	1,190
Ferritin	0.004	0.002	4.366	0.037	1.004	1,000	1,007
PCO_2	0.289	0.132	4.781	0.029	1.335	1,030	1,729
Lymphocyte	-2.690	0.981	7.515	0.006	1.068	1,010	1,464
NLR	0.141	0.040	12.129	0.000	1.151	1,064	1,246
P/F ratio	0.79	0.041	3.834	0.050	1.083	1,000	1,172

The inflammatory cytokine storm, characterized by a sudden and excessive production of proinflammatory cytokines, notably interleukins (IL-6,IL-10), and tumor necrosis factor (TNF-), has been linked to severity and mortality (11). With this in mind, the biochemical examination of plasma inflammatory markers and positive acute phase reactants, including ferritin, may be beneficial in predicting disease development (12). Ahmed et al. (13) found the optimal cutoff value of ferritin 574 ng/mL for predicting mortality in COVID-19 patients. In our study, the cutoff for the prediction of mortality was 648.5 ng/mL, with a sensitivity of 66.7% at the cost of specificity 76.7%. In our study, the ferritin value, which was high in all groups, increased to higher levels (>1000 ng/mL) in the deceased group. Ferritin concentrations in COVID-19 patients were typically within the normal range of less than 400 ng/ml in patients with nonsevere illness, according to Pastora et al. (12) in a systematic study. Hyperferritinemia (ferritin level > 400 g/L) was observed in patients with severe illness at admission, ranging from 1.5 to 5.3 times higher. According to Pastora et al. (12), nonsurvivors had ferritin levels on admission of approximately 1400 ng/mL, which is between 3 and 4 times greater than those reported in survivors.

P/F ratio is the de facto standard for ARDS severity classification since it corresponds to death estimates (14). However, the PaO_2/FIO_2 ratio has limitations: it is not linearly linked to FIO_2 (i.e., the same patient may have varying PaO_2/FIO_2 at various FIO_2) (15). Alfonso et al. (16) found that a P/F ratio below 100 in the ICU was strongly associated with mortality. This study is in parallel with our findings. Although the P/F ratio is used more frequently in ICU admission, we observed that this ratio is meagre and cannot be treated with mechanical ventilation, which may be associated with mortality. Bellan et al. (17) found that the P/F ratio was significantly lower in patients who died than in survivors, indicating more severe respiratory failure at baseline (246 [184-300] vs. 126 [100-202]; <0.001). We found that the P/F ratio AUC was 0.994 and P/F values below 69.75 could be a strong indicator of mortality.

This study has many limitations. Because the hypothesis was based on critical care experience, a retrospective method was used. This limited control in patient selection. Due to the nature of COVID -19 pneumonia, this situation could not be included in the study because different mechanical ventilator settings were used throughout the process.

CONCLUSION

This study showed that in patients with COVID -19, an increase in PCO_2 concentration can predict mortality along with increased ferritin levels, older age, high APACHE scores, low lymphocyte count, elevated NLR and high P/F ratio. The treatment protocols and mortality assessment of COVID -19 patients in the ICU are still not fully elucidated. We hope to shed light on this problem from a different perspective.

ETHICAL DECLARATIONS

Ethics Committee Approval: The study was carried out with the permission of Erzurum Regional Education and Research Hospital Clinical Research Ethics Committee (Date: 20.06.2022, Decision No: 2022/08-96).

Informed Consent: Because the study was designed retrospectively, no written informed consent form was obtained from patients.

Referee Evaluation Process: Externally peer-reviewed.

Conflict of Interest Statement: The authors have no conflicts of interest to declare.

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